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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
BLANCHARD, DAVID J	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 01/20/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/907,907	FISHER ET AL.	
	Examiner	Art Unit	
	David J Blanchard	1642	

-- The MAILING DATE f this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *22 and 85* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22 and 85* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Election/Restrictions

1. Claims 22 and 85 are pending.

2. Applicant's election of Group III, claim 22 in the Paper filed 10/23/2003 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

3. Claims 1-21 and 23-84 were cancelled in the Paper filed 10/23/2003.

4. Claim 85 has been added in the Paper filed 10/23/2003.

5. Claims 22 and 85 are under examination.

Specification

6. The disclosure is objected to because of the following informalities:

a. The Brief Description of the Figures does not adequately describe Figure 10. Specifically, Figure 10 have parts A and B, however, the Brief Description of the Figures does not describe part A and part B for Figures 10 (see the amendment filed 9/4/2002).

b. The abstract of the disclosure is objected to because the abstract does not reflect the claimed subject matter. The abstract should be restricted to the claimed subject matter. Correction is required. See MPEP § 608.01(b).

c. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. Applicant should restrict the title to the claimed invention.

Appropriate correction is required.

Claim Rejections - 35 USC § 101

7. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

8. Claims 22 and 85 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a substantial asserted utility or a well-established utility.

Claims 22 and 85 are drawn to a monoclonal antibody or antigen binding fragments thereof that binds a protein having an amino acid sequence of SEQ ID NO:42 and a protein that is inducible by interferon β (IFN-β). The specification discloses genes expressed during the induction of irreversible growth arrest and terminal differentiation in human melanoma cells using differentiation induction subtraction hybridization. Using this approach and subsequent Northern and reverse Nrothern blotting analyses differentially expressed cDNAs were identified and one of these cDNAs, Old-35 was restricted to terminal differentiation and senescence (see pages 2-3). The specification asserts "Due to the high sequence homology of Old-35 to bacterial polyribonucleotide

phosphorylase (PNPase), it is possible that Old-35 protein may exhibit a PNPase enzymatic activity" (see page 36-37 and Figure 10A-10B).

The assertion that the disclosed protein has a biological activity associated with PNPase (i.e., RNA degradation in growth arrested cells) is not substantial in the absence of supporting evidence. The relevant literature reports numerous examples of polypeptide families wherein individual members have distinct, and even opposite, biological activities. For example, Tischer et al. (U.S. Patent 5,194,596) establishes that VEGF (a member of the PDGF, or platelet-derived growth factor, family) is mitogenic for vascular endothelial cells but not for vascular smooth muscle cells, which is opposite to the mitogenic activity of naturally occurring PDGF, which is mitogenic for vascular smooth muscle cells but not for vascular endothelial cells (column 2, line 46 to column 3, line 2). The differences between PDGF and VEGF are also seen *in vivo*, wherein endothelial-pericyte associations in the eye are disrupted by intraocular administration of PDGF but accelerated by intraocular administration of VEGF (Benjamin et al., 1998, Development 125:1591-1598; see Abstract and pp. 1594-1596). Vukicevic et al. (1996, PNAS USA 93:9021-9026) disclose that OP-1, a member of the TGF-β family of proteins, has the ability to induce metanephrogenesis, whereas closely related TGF-β family members BMP-2 and TGF-β1 had no effect on metanephrogenesis under identical conditions (p. 9023, paragraph bridging columns 1-2). See also Massague, who reviews other members of the TGF-β family (1987, Cell 49:437-8, esp. p. 438, column 1, second full paragraph to the end). Similarly, PTH and PTHrP are two structurally closely related proteins, which can have opposite effects on bone resorption

(Pilbeam et al., 1993, Bone 14:717-720; see p. 717, second paragraph of Introduction). Finally, Kopchick et al. (U.S. Patent 5,350,836) disclose several antagonists of vertebrate growth hormone that differ from naturally occurring growth hormone by a single amino acid (column 2, lines 37-48). Yehudai-resheff et al (2001, Mol. Cell. Biol. 21(6):5408-5416) teach a polynucleotide phosphorylase (PNPase) in spinach cloroplasts having two distinct acitivites (1) PNPase is able to polyadenylate RNA molecules and (2) PNPase functions in exonucleolytic degradation of RNA (see page 5408). Accorsi et al (1991, Biochem. Int. 24(1):23-31) teach human red cell lysates containing a purine-nucleoside phosphorylase (PNPase) with progressive post-translational modifications that affect the allosteric activation by the inosine substrate (see pages 27-30). Both G. W. (U.S. Patent 6,020,172, 02/01/2000) teach that PNPase metabolizes the pro-drug 6-methyl-purine-2'deoxyribonucleoside to the toxic product 6MP, which is toxic to cells and other compounds such as arabinofuranosyl-2-fluoroadenine (Fludarabine) could also be used as substrates for PNPase (see column 8, lines 52-54 and column 9, lines 9-11). The instant disclosure only speculates as to what activity the "Old-35" may have based on homology with a bacterial PNPase "it is possible that Old-35 protein may exhibit a PNPase enzymatic activity" (see page 36, lines 29-32).

Generally, the art acknowledges that function cannot be predicted based solely on structural similarity to a protein. For example, Skolnick et al. (2000, Trends in Biotech. 18:34-39) state that knowing the protein structure by itself is insufficient to annotate a number of functional classes, and is also insufficient for annotating the

specific details of protein function (see Box 2, p. 36). Smith et al. (1997, Nature Biotechnology 15:1222-1223) remark that there are numerous cases in which proteins having very different functions share structural similarity due to evolution from a common ancestral gene. Brenner (1999, Trends in Genetics 15:132-133) argues that accurate inference of function from homology must be a difficult problem since, assuming there are only about 1000 major gene superfamilies in nature, then most homologs must have different molecular and cellular functions (see page 132). Thus, the specification fails to support the asserted substantial utility.

The specification does not support a substantial utility regarding the claimed antibodies that bind Old-35 for purposes unrelated to the asserted biological activity. For example, the specification asserts that the antibodies of the instant invention have immediate use as exemplified by methods of monitoring the progress of chemotherapy via monitoring Old-35 expression, the expression of Old-35 indicating that the chemotherapy is effective (see page 23, lines 36-37 and page 24, lines 1-3). The specification does not exemplify any method or describe any particular cancerous condition in which the monitoring of Old-35 expression with an antibody will provide information as to the status of the particular cancer during chemotherapy. The specification further asserts that antibodies that bind Old-35 would have utility as a diagnostic for assessing the proliferating stage of a tumor (see page 24, lines 17-19) or the antibodies may be used as an inhibitor of Old-35 function and activity by binding to the active sites on Old-35, thereby stimulating or resuming cell growth (see page 23, lines 5-18). The specification does not disclose a correlation between any specific

disorder and an altered level or form of the Old-35 polypeptide wherein an antibody that binds the Old-35 polypeptide has diagnostic utility or utility in a method for inhibiting the activity of the Old-35 protein related to a specific disorder. Also, the specification does not predict whether the claimed Old-35 polypeptide would be overexpressed or underexpressed in a specific, diseased tissue compared to the healthy tissue control.

The instant application provides insufficient guidance or direction as to how one of skill in the art could use the claimed antibodies that bind Old-35 in a way that constitutes a ~~credible, specific and~~ substantial utility. The proposed uses of the claimed invention are simply starting points for further research and investigation into potential practical uses of the claimed antibodies. As stated on page 4, lines 23-28 of the specification "Further experimentation is required to define the precise role of Old-35 in interferon signaling, terminal differentiation and cellular senescence. Full-length cloning and subsequent protein analysis should provide insights into the function of this potentially important gene in the processes of aging and differentiation." (see page 4, lines 23-28). "Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing." *Brenner v. Manson*, 148 USPQ at 696.

9. Claims 22 and 85 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention without undue experimentation.

Claim Rejections - 35 USC § 112

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 22 and 85 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. This is a NEW MATTER rejection and not written description.

NEW MATTER has been added to the claims via amending claim 22 to recite a limitation directed to "(ii) a protein that is inducible by interferon beta" due to lacking a connection between protein induction and interferon beta. It appears that applicants are relying on the growth suppressive effect of interferon beta on HO-1 cells, as well as increased mRNA stability of Old-35 during confluence and senescence to support the recited limitation "a protein that is inducible by interferon beta (see page 4, lines 19-23). It is acknowledged that Figure-1 discloses interferon beta induction of Old-35 RNA, however, a protein that is induced by interferon beta does not appear to be disclosed. Support for interferon beta and induction of protein expression cannot apparently be

found in the originally filed claims, specification or drawings and Applicants have not pointed out where support for this limitation can be found.

12. Claims 22 and 85 are rejected under 35 U.S.C. 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required are summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The claims are drawn to a monoclonal antibody or antigen binding fragments thereof that bind a protein having an amino acid sequence of SEQ ID NO:42 and a protein that is inducible by interferon β (IFN-β).

The specification teaches genes expressed during the induction of irreversible growth arrest and terminal differentiation in human melanoma cells using differentiation induction subtraction hybridization. Using this approach and subsequent Northern and reverse Nrothern blotting analyses differentially expressed cDNAs were identified and one of these cDNAs, Old-35 was restricted to terminal differentiation and senescence

(see pages 2-3). The specification also teaches that the Old-35 gene encodes a polypeptide (SEQ ID NO:42) that shares homology with bacterial polyribonucleotide phosphorylase (see page 36, lines 29-32 and Figure 10A-10B).

The specification does not disclose any particular disease state or condition correlated with altered expression of Old-35 mRNA or protein nor does the specification provide guidance to assist the skilled artisan on how to make and use antibodies that bind the Old-35 polypeptide as a diagnostic or therapeutic tool.

The specification does not reasonably provide enablement for antibodies that bind the Old-35 protein or pharmaceutical compositions comprising such based on the written disclosure alone. Those of skill in the art recognize that expression of mRNA, specific for a tissue type, does not necessarily correlate nor predict equivalent levels of polypeptide expression. In fact, evidence abounds in which protein levels do not correlate with steady-state mRNA levels or alterations in mRNA levels. For example, Fu et al (EMBO Journal, 1996, Vol. 15, pp. 4392-4401) teach that levels of p53 protein expression do not correlate with levels of p53 mRNA levels in blast cells taken from patients with acute myelogenous leukemia, said patients being without mutations in the p53 gene. Further, Powell et al (Pharmacogenetics, 1998, Vol. 8, pp. 411-421, abstract) teach that mRNA levels for cytochrome P450 E1 did not correlate with the level of corresponding protein, and conclude that the regulation of said protein is highly complex. Vallejo et al (Biochimie, 2000, vol. 82, pp. 1129-1133, abstract) teach that no correlation was found between NRF-2 mRNA and protein levels suggesting post-transcriptional regulation of NRF-2 protein levels. Lewin (Genes VI, 1997, CH. 29, pp.

847-848) states "But having acknowledged that control of gene expression can occur at multiple stages, and that production of RNA cannot inevitably be equated with production of protein, it is clear that overwelming majority of regulatory events occur at the initiation of transcription" (see page 847, right column). These references serve to demonstrate that the analysis of levels of polynucleotide transcripts cannot be relied upon to anticipate levels of protein expression. Further, Jang et al (Clinical and Experimental Metastasis, 1997, vol. 15, pp. 469-483, abstract) teach that further studies are necessary to determine if changes in protein levels track with changes in mRNA levels for metastasis associated genes in murine tumor cells, thus providing further evidence that one of skill in the art cannot anticipate that the level of a specific mRNA expressed by a cell will be paralleled at the protein level due to complex homeostatic factors controlling translation and post- translational modification.

Thus, the predictability of protein translation and its possible utility as a diagnostic or therapeutic target are not necessarily contingent on the levels of mRNA expression due to the multitude of homeostatic factors affecting transcription and translation. Therefore, absent evidence of the Old-35 protein expression, including the correlation to a diseased state or condition, one of skill in the art would not be able to predictably make and use antibodies that bind the Old-35 polypeptide in pharmaceutical compositions as a diagnostic or therapeutic tool. The specification does not predict or show whether the Old-35 polypeptide would be over-expressed or under-expressed in a specific, diseased tissue compared to a healthy tissue control. In the absence of a direct correlation between the up regulation of transcription and translation of the Old-35

polypeptide associated with a disease state, one of ordinary skill in the art would be unable to make and use antibodies specific for the Old-35 polypeptide as a pharmaceutical composition.

No guidance or nexus between any particular disease state and Old-35 protein expression is provided to assist one skilled in the art to make and use Old-35 specific antibodies. The scope of the claims must bear a reasonable correlation with the scope of enablement. See In re Fisher, 166 USPQ 19 24 (CCPA 1970).

In view of the lack of predictability of the art to which the invention pertains as evidenced by Fu et al., Powell et al., Vallejo et al., Lewin B., Jang et al. and lack of guidance in the specification related to using antibodies that specifically react with the Old-35 protein correlated to a specific disease state or condition, undue experimentation would be required to practice the claimed antibodies as a pharmaceutical composition with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed invention and absent working examples providing evidence which is reasonably predictive that the claimed Old-35 antibodies are effective diagnostic or therapeutic tools.

Conclusion

13. No claim is allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Blanchard whose telephone number is (571)

272-0827. The examiner can normally be reached at (571) 272-0827 from 8:00 AM to 5:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony C. Caputa, can be reached at (571) 272-0829. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1123.

Official papers related to this application may be submitted to Group 1600 by facsimile transmission. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The official fax number for Group 1600 where this application or proceeding is assigned is (703) 872-9306.

Respectfully,
David J. Blanchard
703-605-1200